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EXAMINER

RUSSEL, JEFFREY E

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UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte STEPHEN B. H. KENT, TOM W. MUIR and
PHILIP E. DAWSON

Appeal 2007-4180
Application 09/710,633
Technology Center 1600

Decided: March 12, 2008

Before TONI R. SCHEINER, ERIC GRIMES and JEFFREY N.
FREDMAN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for producing a protein. The Examiner has rejected the claims as lacking adequate written description in the Specification. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

BACKGROUND

“Chemical synthesis of proteins has ... contributed to the exploration of the relationship of protein structure to function” (Spec. 2). The Specification discloses that one method of chemical synthesis entails

“chemoselective reaction of unprotected peptides to give a product with an unnatural backbone structure at the ligation site” (*id.* at 3), and that “[u]se of unprotected peptides circumvented the difficulties inherent to classical chemical synthesis, viz[.] complex combinations of protecting groups that lead to limited solubility of many synthetic intermediates” (*id.* at 3-4). The Specification also discloses that “[w]hat is needed is a technique of native chemical ligation which combines the formation of a native peptide bond at the ligation site with the advantages of chemoselective reaction of unprotected peptides” (*id.* at 6).

The Specification also discloses the chemical synthesis of proteins and large oligopeptides by “chemoselective reaction of an unprotected synthetic peptide- α -thioester with another unprotected peptide segment containing an N-terminal Cys residue, to give a thioester-linked intermediate. . . . [T]his intermediate undergoes spontaneous, rapid intramolecular reaction to form a native peptide bond at the ligation site” (*id.* at 7).

DISCUSSION

1. CLAIMS

Claims 11-14 and 32 are on appeal. Claims 8, 10, 24, 26, and 29-31 have been indicated to be allowable (Office action mailed December 8, 2003, page 3). Claims 11 and 32 are representative of the rejected claims. Claims 11 and 32, along with independent claim 8, read as follows:

Claim 8: A method for producing a desired protein or domain thereof, which comprises admixing:

(I) a first oligopeptide, said first oligopeptide comprising a fragment of said desired protein or domain thereof, and having a C-terminal thioester; and

(II) a second oligopeptide, said second oligopeptide comprising a fragment of said desired protein or domain thereof, and having an N-terminal cysteine amino acid residue having an unoxidized sulfhydryl side chain and a free amino group that is capable of forming a 13-aminothioester linkage with said C-terminal thioester that rearranges to form an amide bond therein between;

wherein said admixing is conducted under conditions sufficient to permit the formation of an amide bond between the C-terminus of said first oligopeptide and the N-terminus of said second oligopeptide,

Claim 11: The method of claim 8, wherein said desired protein is a derivative of a naturally isolatable protein that contains one or more variant residues that are not found in said naturally isolatable protein.

Claim 32: A method for producing a desired protein or domain thereof, which comprises admixing:

(I) a first oligopeptide, said first oligopeptide comprising a fragment of said desired protein or domain thereof, and having a C-terminal thioester; and

(II) a second oligopeptide, said second oligopeptide comprising a fragment of said desired protein or domain thereof, and having an N-terminal cysteine amino acid residue having an unoxidized sulfhydryl side chain and a free amino group that is capable of forming a β -aminothioester linkage with said C-terminal thioester that rearranges to form an amide bond therein between;

wherein said admixing is conducted under conditions sufficient to permit the formation of an amide bond between the C-terminus of said first oligopeptide and the N-terminus of said second oligopeptide;

wherein said desired protein is a derivative of a naturally isolatable protein, said desired protein containing one or more cysteine residues that are not found in said naturally isolatable protein.

2. WRITTEN DESCRIPTION

Claims 11-14 and 32 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that they lack an adequate written description in the Specification.

The Examiner finds that the Specification does not adequately describe the claimed invention because “there is no original disclosure of derivatives of naturally isolatable proteins containing one or more variant or cysteine residues that are not found in the naturally isolatable protein” (Answer 4). The Examiner further finds that the “original disclosure does not include the concept of altering a naturally-occurring protein’s amino acid sequence by replacing amino acids with variant residues or cysteine residues . . . so that a derivative of the naturally-occurring protein can be synthesized by the disclosed method” (*id.*).

Appellants argue that a “protein containing a cysteine residue that is not found in the naturally isolatable protein is disclosed in the specification at Example 4 . . . and illustrated in Scheme 9” (App. Br. 5). Appellants note that Scheme 9 is entitled “Mutant HIV-1 K41 Protease Synthesized by Native Chemical Ligation” and argue that “[i]t would be well understood by one skilled in the relevant art that the term ‘Mutant HIV-1 K41 Protease’ means that a mutation has occurred at position 41.” (*id.*). Specifically, Appellants argue that Scheme 9 shows native chemical ligation between two oligopeptides, one of which has a Cys-for-Lys substitution at position 41, “to form the 1-99 product having a cysteine at position 41” (*id.*).

Appellants further argue that a description of proteins containing variant residues is found in the Specification “as follows:

‘The general synthetic access provided by the method of native chemical ligation greatly expands the scope of variation of the covalent structure of the protein molecule.’ (Specification, page 7, bottom of first paragraph.)

‘It [native chemical ligation] provides for unrestricted variation of protein covalent structure made possible by general synthetic access, and provides new impetus to exploration of the structural basis of properties such as folding, stability, catalytic activity, binding, and biological action.’ (Specification, page 21, second paragraph.)”

(App. Br. 7).

We agree with Appellants that the Examiner has not adequately explained why a person skilled in the art would not consider the Specification to provide adequate descriptive support for the disputed limitations. The purpose of the written description requirement is to “ensure that the scope of the right to exclude, as set forth in the claims does not overreach the scope of the inventor’s contribution to the field as far as described in the patent specification.” *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000). The Examiner

“bears the initial burden . . . of presenting a *prima facie* case of unpatentability.” *In re Oetiker*, 977 F.2d 1443, 1445, (Fed. Cir. 1992). Insofar as the written description requirement is concerned, that burden is discharged by “presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.” . . . If . . . the specification contains a description of the claimed invention, albeit not *in ipsius verbis* (in the identical words), then the examiner . . . , in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient.

In re Alton, 76 F.3d 1168, 1175 (Fed. Cir. 1996).

In our view, the Specification would have conveyed to those of skill in the art that the inventor was in possession at the time the application was filed of the claimed generic methods for producing a desired protein that

contains one or more variant residues (claim 11) or cysteine residues (claim 32) that are not found in the naturally isolatable protein.

With respect to non-naturally occurring cysteine residues, as set forth above, the Specification discloses the chemical synthesis of proteins by “chemoselective reaction of an unprotected synthetic peptide- α -thioester with another unprotected peptide segment containing an N-terminal Cys residue, to give a thioester-linked intermediate,” which “undergoes spontaneous, rapid intramolecular reaction to form a native peptide bond at the ligation site” (Spec. 7). The Specification also provides an example involving ligation of a peptide that deviates from the natural form in containing a cysteine as a substitute for a lysine, where the substitution was made to allow a ligation reaction (*id.* at Example 4). Given this disclosure, one of skill in the art would appreciate the absolute requirement for a cysteine for the peptide ligation reaction and would understand that, for the synthesis of some proteins, modifying the native sequence by substituting or inserting cysteine residues in the protein would facilitate protein synthesis.

We also agree with Appellants that the Specification reasonably appears to describe the claimed method with respect to synthesizing proteins with other variant amino acid residues. The Specification describes the disclosed method as providing “general synthetic access . . . [that] greatly expands the scope of variation of the covalent structure of the protein molecule” (Spec. 7). In addition, the Specification also discloses that the claimed method “provides for unrestricted variation of protein covalent structure made possible by general synthetic access, and provides new impetus to exploration of the structural basis of properties such as folding,

stability, catalytic activity, binding, and biological action” (Spec. 21). Given these disclosures, one of skill in the art would understand that one of the advantages of the claimed method is the means for varying protein structure; i.e., producing variant proteins that contain one or more variant residues that are not found in the naturally isolatable protein.

Because we agree with Appellants that the totality of the record does not support the Examiner’s rejection, the rejections of claims 11-14 and 32 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description is reversed.

REVERSED

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